



Febuxostat Therapy for Patients with Gout and Stage 2–4 CKD: a Retrospective Study

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ABSTRACT

Introduction: The aim of this study is to explore the efficacy and renal safety of febuxostat in gout and stage 2–4 chronic kidney disease (CKD) and factors that correlated with target serum urate (SU).

Methods: A single-center retrospective study including male patients with gout and CKD was conducted. SU, the rate of SU < 360 μmol/L (RAT), and renal safety were analyzed in subjects who received febuxostat over 44 weeks. Factors that correlated with target SU were also explored.

Peiyu Zhang and Mo Chen contributed equally to this work.

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Results: Between January 2017 and March 2021, 102 patients (stage 2 CKD: $n = 27$; stage 3 CKD: $n = 70$; stage 4 CKD: $n = 5$) were enrolled. The SU level reduced significantly over 44 weeks (600.76 ± 95.42 versus 405.52 ± 111.93 μmol/L; $P < 0.05$), and RAT increased to 39.20%. The overall estimated glomerular filtration rate (eGFR) level improved over 44 weeks (52.05 ± 11.68 versus 55.46 ± 14.49 mL/min/1.73 cm², $P < 0.05$). An obvious improvement of eGFR was observed in stage 3 CKD, in patients with ≤ 1 risk factor (hypertension, diabetic mellitus, hyperlipidemia, or usage of non-steroidal anti-inflammatory drugs), and in patients with terminal SU < 360 μmol/L ($P < 0.05$). Logistic regression analysis indicated that baseline SU level and body weight were correlated with RAT. Further analysis revealed that patients with SU < 600 μmol/L and body weight ≤ 70 kg reached higher RAT (56.7%).

Conclusions: Febuxostat demonstrated efficacy and renal safety in patients with gout and CKD in clinical practice. Achieving the target SU could obviously improve renal function. Baseline SU level and body weight could affect the achievement of target SU.

Keywords: Chronic kidney disease; Febuxostat; Gout; Renal safety; Target serum urate

Key Summary Points

Why carry out this study?

Febuxostat is recommended as the first-line therapy for gout, but evidence in patients with gout and CKD is relatively lacking, especially regarding renal outcomes and risk factors associated with target SU.

The aim of this study is to investigate the renal effect of febuxostat in patients with gout and CKD and explore the risk factors that may affect the achievement of target SU.

What was learned from the study?

An obvious improved eGFR was observed in stage 3 CKD and in patients who achieved target SU.

This is the first study to explore the renal benefit of “treat to target” therapy with febuxostat in patients with gout and CKD and the risk factors associated with achieving target SU in these patients. The study may provide evidence for the management of patients with gout and CKD in clinical practice.

INTRODUCTION

Gout is an inflammatory joint disease caused by chronic deposition of monosodium urate (MSU) crystals in joints [1]. Hyperuricemia is the primary stage of gout. Elevated serum urate (SU) level can cause structural and functional damage to the kidney, resulting in nephrolithiasis or kidney injury [2]. Notably, renal impairment is an important risk factor for hyperuricemia (HUA) and may exacerbate the severity of gout by decreasing SU excretion [3].

Studies have reported that patients with SU concentration > 9 mg/dL or moderate-to-severe chronic kidney disease (CKD) had a higher risk

of gout progression [4, 5], indicating that urate-lowering treatment (ULT) and renal function protection are important for patients with gout and CKD. There is a consensus recommendation that ULT should be introduced at an early stage of gout and CKD, representing regular management of patients and maintaining SU level less than 360 $\mu\text{mol/L}$ [6]. Xanthine oxidase inhibitors (XOIs) and uricosurics are the main urate-lowering drugs [7]. Allopurinol is associated with severe hypersensitivity reaction in Asians and dosage adjustment in CKD, whereas benzbromarone is contraindicated in patients with history of nephrolithiasis and may also aggravate the risk of nephrolithiasis. Thus, febuxostat is more widely used, especially in patients with gout and CKD.

Previous studies have reported that febuxostat had a good urate-lowering effect in patients with gout and CKD, but its effect on renal function remains unclear [8–11]. Emerging reviews or meta-analyses have demonstrated that febuxostat has a renoprotective effect in CKD patients with HUA [12, 13]. While promising, these results may not be directly applicable to patients with gout, because the conditions of this disease are more severe than HUA, considering the multisystem damage and persistent inflammation seen in gout [1]. Limited studies have reported the renal safety of febuxostat [8–11]. However, the findings are unlikely to be widely adopted in complex clinical practice due to their small sample size and controversial conclusions. There is thus a clinical need to clarify the renal effect of febuxostat in patients with gout and CKD.

The aim of this retrospective study is to explore the efficacy of febuxostat and its associated risk factors, and to determine whether ULT with febuxostat results in improved estimated glomerular filtration rate (eGFR) in patients with gout and CKD in clinical practice.

METHODS

Study Design and Approval

The current study was a single-center retrospective study conducted in the Rheumatology

Department of the Second Affiliated Hospital of Zhejiang University School of Medicine. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval no. 2021-0409). The requirement for written informed consent was waived by the Ethics Committee owing to the retrospective nature of the study. The study was conducted in accordance with the Helsinki Declaration and in full compliance with current legislation for retrospective studies.

Patients

Participants were enrolled from the Rheumatology Department of the Second Affiliated Hospital of Zhejiang University School of Medicine from January 2017 to March 2021. Patients who met the following criteria were included in the study: (i) male, aged ≥ 18 and ≤ 80 years, diagnosed with primary gout and CKD; (ii) treated with febuxostat continuously over 44 weeks; (iii) baseline SU ≥ 420 $\mu\text{mol/L}$ and serum creatinine (sCr) ≥ 106 $\mu\text{mol/L}$. The exclusion criteria included: (i) patients with severe liver injury, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level > 3 times the upper limit of the normal range; (ii) patients receiving two kinds of urate-lowering drugs; (iii) patients without laboratory test results at baseline and ~ 44 weeks; (iv) patients with acute kidney injury; (v) patients with cancer, renal transplantation, or on dialysis before the index date.

The index date was defined as the date of the first febuxostat prescription at the beginning of regular follow-up. In our clinical practice, the urate-lowering therapy escalation protocol was that febuxostat was widely started at 20–40 mg daily and adjusted at each visit (at a dosage dependent on SU), to a maximum dosage of 80 mg daily. Study participants with gout were classified according to the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Gout Classification Criteria, and the target SU for ULT was defined as less than 360 $\mu\text{mol/L}$ [7, 14, 15]. The rate of

achieving target SU (RAT) was defined according to previous study [16]. The CKD diagnosis and stage classification were defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [17]. Renal function was assessed by eGFR, according to the simplified versions of the Modification of Diet in Renal Disease (MDRD) study equation as shown below [18, 19]:

$$\text{Male: eGFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{sCr}/88.402)^{-1.154} \times \text{Age}^{-0.203}$$

sCr: serum creatinine ($\mu\text{mol/L}$).

Data Source

The electronic medical records system (EMRS) includes patients' general information, diagnosis, prescription, laboratory data, and outpatient and inpatient information. The patients' data were retrieved from the EMRS, including clinical information (age, history of gout, comorbidities, tophus, and gout flares at baseline and during follow-up), prescriptions (including concomitant medications), and laboratory results (SU, sCr, etc.).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, USA) software for Windows. All analyses were two-sided, and $P < 0.05$ was considered statistically significant. Continuous variables are presented as mean \pm standard deviation (SD), and t test, one-way analysis of variance (ANOVA)–Scheffe test, post hoc test (ANOVA-LSD), and repeated-measures ANOVA were used to evaluate differences. Qualitative variables are expressed as frequency (%), and the chi-squared test was used to evaluate the significance. Univariate logistic regression analysis was initially used to identify candidate risk factors for reaching target SU, and then multivariate logistic regression analysis was performed on significant variables. All figures were generated using GraphPad Prism 8 (GraphPad Software, USA).

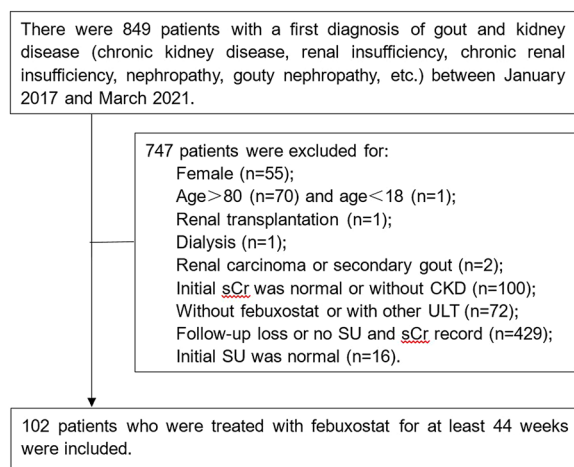


Fig. 1 Flow diagram of study participants. *sCr* serum creatinine, *CKD* chronic kidney disease, *SU* serum urate, *ULT* urate-lowering treatment

RESULTS

Participant Characteristics

A total of 849 patients were diagnosed with gout and kidney disease between January 2017 and March 2021. Subsequently, 747 were excluded after screening clinical information, prescriptions, and laboratory data. A total of 102 patients were therefore included in the final analysis. The participant flow through the study is shown in Fig. 1. Their baseline characteristics are presented in Table 1. Among the 102 subjects, 27 (26.47%) were diagnosed with stage 2 CKD, 70 (68.63%) with stage 3 CKD, and 5 (4.90%) with stage 4 CKD. The SU was significantly higher in stage 4 CKD compared with stage 2 or stage 3 CKD ($P < 0.05$). Notably, according to the most recent records, about 40% patients were followed for longer than 52 weeks.

Levels of SU, *sCr*, *eGFR*, and RAT after ULT with Febuxostat

Over the study period, the overall SU was significantly decreased after ULT with febuxostat ($600.76 \pm 95.42 \mu\text{mol/L}$ versus

$405.52 \pm 111.93 \mu\text{mol/L}$; $P < 0.05$). The SU for different stages of CKD was also significantly decreased ($P < 0.05$; Fig. 2A, D and Table S1).

The *sCr* was decreased and the *eGFR* was increased for all subjects over 44 weeks (*sCr*: $138.58 \pm 41.57 \mu\text{mol/L}$ versus $132.83 \pm 43.53 \mu\text{mol/L}$, *eGFR*: $52.05 \pm 11.68 \text{ mL/min/1.73 m}^2$ versus $55.46 \pm 14.49 \text{ mL/min/1.73 m}^2$; $P < 0.05$) (Fig. 2B, C and Table S1). The *sCr* and the *eGFR* in stage 2 CKD patients were relatively stable (*sCr*: $111.56 \pm 3.64 \mu\text{mol/L}$ versus $111.04 \pm 18.32 \mu\text{mol/L}$, *eGFR*: $64.44 \pm 3.44 \text{ mL/min/1.73 m}^2$ versus $66.55 \pm 11.76 \text{ mL/min/1.73 m}^2$; $P > 0.05$). The *sCr* and the *eGFR* in stage 3 CKD patients were significantly improved within 36 weeks (*sCr*: $138.87 \pm 23.79 \mu\text{mol/L}$ versus $123.79 \pm 25.09 \mu\text{mol/L}$, *eGFR*: $49.38 \pm 7.97 \text{ mL/min/1.73 m}^2$ versus $57.81 \pm 13.47 \text{ mL/min/1.73 m}^2$; $P < 0.05$), but this slightly reversed over 44 weeks (*sCr*: $132.02 \pm 26.78 \mu\text{mol/L}$, *eGFR*: $53.24 \pm 11.62 \text{ mL/min/1.73 m}^2$; $P < 0.05$). The *sCr* and the *eGFR* in stage 4 CKD patients were improved significantly within 36 weeks (*sCr*: $280.40 \pm 60.90 \mu\text{mol/L}$ versus $198.00 \pm 83.44 \mu\text{mol/L}$, *eGFR*: $22.48 \pm 4.28 \text{ mL/min/1.73 m}^2$ versus $34.75 \pm 15.12 \text{ mL/min/1.73 m}^2$; $P < 0.05$), while improvement was not obvious over 44 weeks (*sCr*: 261.92 ± 96.21 , *eGFR*: 26.70 ± 11.11 , $P > 0.05$) (Fig. 2E, F and Table S1).

Among 102 participants, 40 reached the target SU ($\text{SU} < 360 \mu\text{mol/L}$) and the overall RAT increased up to 39.20% at the end of the study. After classification of CKD by *eGFR*, the RAT fluctuated significantly over time and reached up to 33.30%, 41.40%, and 40.00% for stage 2, stage 3, and stage 4 CKD patients, respectively (Fig. 3A and Table S1). Consecutively, the overall participants were divided into two subgroups according to terminal SU. The *eGFR* in both groups was improved, especially in the group with terminal $\text{SU} \geq 360 \mu\text{mol/L}$ group: 52.83 ± 11.71 versus 54.41 ± 14.64 , $P > 0.05$; terminal $\text{SU} < 360 \mu\text{mol/L}$: 50.83 ± 11.68 versus 57.08 ± 14.28 , $P < 0.05$). There was statistical difference between the two groups ($P < 0.05$). (Fig. 3B and Table S2).

Table 1 Baseline characteristics of subjects

	All	CKD2	CKD3	CKD4
Total, No. (%)	102	27 (26.47%)	70 (68.63%)	5 (4.90%)
Follow-up time, weeks	51.97 ± 6.26	52.21 ± 5.43	51.64 ± 6.19 [#]	55.31 ± 11.01
Age, years	59.15 ± 12.68	51.30 ± 12.25	62.21 ± 11.29	58.60 ± 17.47
Gout duration, years	8.99 ± 7.68	6.86 ± 6.21	9.61 ± 7.87	11.40 ± 10.95
Family history of gout, No. (%)	8 (7.80%)	0 (0.00%)	5 (7.10%)	3 (60.00%) ^{#*}
Gout flares (baseline, %)	51 (50.00%)	11 (40.7%)	37 (52.9%)	3 (60.00%)
Body weight, kg	70.57 ± 9.49	74.69 ± 11.15	68.90 ± 8.04 [#]	71.50 ± 13.41
BMI, kg/m ²	24.68 ± 3.09	25.58 ± 3.84	24.32 ± 2.66	24.76 ± 3.97
Systolic pressure, mmHg	138.84 ± 19.96	141.17 ± 21.66	139.16 ± 19.82	126.80 ± 12.99
Diastolic pressure, mmHg	81.86 ± 13.61	87.78 ± 18.86	80.52 ± 11.31 [#]	76.20 ± 12.09
Tophus, No. (%)	38 (37.30%)	9 (33.30%)	27 (38.60%)	2 (40.00%)
Comorbid conditions, No. (%)				
Hypertension	57 (55.90%)	10 (37.00%)	43 (61.40%) [#]	4 (80.00%)
Diabetic mellitus	12 (11.80%)	3 (11.10%)	9(12.90%)	0 (0.00%)
Hyperlipidemia	35 (34.30%)	9 (33.30%)	24(34.30%)	2 (40.00%)
Cardio-cerebrovascular disease	9 (8.80%)	1 (3.70%)	8 (11.40%)	0 (0.00%)
Concomitant medication use, No. (%)				
Colchicine	31 (30.40%)	5 (18.50%)	24 (34.30%)	2 (40.00%)
NSAIDs	8 (7.80%)	4 (14.80%)	4 (5.70%)	0 (0.00%)
Glucocorticoid	65 (63.70%)	15 (55.60%)	47 (67.10%)	3 (60.00%)
Previous ULT, No. (%)				
None	64 (62.70%)	16 (59.30%)	45(64.30%)	3 (60.00%)
Febuxostat	21 (20.60%)	6 (22.20%)	14 (20.00%)	1 (20.00%)
Allopurinol	13 (12.70%)	4 (14.80%)	8 (11.40%)	1 (20.00%)
Benzbromarone	4 (3.90%)	1 (3.70%)	3 (4.30%)	0 (0.00%)
Initial dosage of febuxostat, No. (%)				
10–40 mg/day	70 (68.70%)	20 (74.10%)	48 (68.50%)	2 (40.00%)
40 mg/day	27(26.50%)	7 (25.90%)	17 (24.30%)	3 (60.00%)
40–80 mg/day	5 (4.90%)	0 (0.00%)	5 (7.20%)	0 (0.00%)
Laboratory data, mean ± SD				
SU, μmol/L	600.76 ± 95.42	584.56 ± 88.55	599.31 ± 90.11	708.60 ± 150.08 ^{#*}
eGFR, mL/min/1.73 m ²	52.05 ± 11.68	64.44 ± 3.44	49.38 ± 7.97 [#]	22.48 ± 4.28 ^{#*}
sCr, μmol/L	138.58 ± 41.57	111.56 ± 3.64	138.87 ± 23.79 [#]	280.40 ± 60.90 ^{#*}

Table 1 continued

	All	CKD2	CKD3	CKD4
Nephrolithiasis, No. (%)	51 (50.00%)	15 (55.50%)	33 (47.10%)	3 (60.00%)
Tophus for DECT, No. (%)	26 (25.50%)	5 (18.5%)	21 (30.00%)	NA
Medical insurance (yes, %)	71 (69.60%)	19 (70.40%)	50 (71.40%)	2 (40.00%)
Occupation				
Retired	11 (10.80%)	1 (3.70%)	9 (12.90%)	1 (20.00%)
Worker	25 (24.50%)	11 (40.70%)	12 (17.10%)	2 (40.00%)
Self-employed entrepreneur	63 (61.80%)	15 (55.60%)	46 (65.70%)	2 (40.00%)
Farmer	3 (2.90%)	0 (0.00%)	3 (4.30%)	0 (0.00%)
Residence				
Hangzhou City	67 (65.70%)	19 (70.40%)	47 (67.10%)	1 (20.00%)
[§] Zhejiang Province	22 (21.60%)	4 (14.80%)	16 (22.90%)	2 (40.00%)
Outside Zhejiang Province	13 (12.70%)	4 (14.80%)	7 (10.00%)	2 (40.00%)

BMI body mass index, calculated as weight in kilograms divided by height in meters squared, *NSAIDs* non-steroidal anti-inflammatory drugs, *ULT* urate-lowering treatment, *SU* serum urate, *eGFR* estimated glomerular filtration rate, *sCr* serum creatinine, *NA* not available, *DECT* dual-energy computed tomography

* $P < 0.05$, stage 3 CKD versus stage 4 CKD

$P < 0.05$, stage 2 CKD versus stage 3 CKD or stage 2 CKD versus stage 4 CKD

[§]Zhejiang Province: patients from others areas of Zhejiang Province besides Hangzhou City

Stratification Analysis of SU, sCr, and eGFR on the Basis of Hypertension, Diabetic Mellitus, Hyperlipidemia, and Use of NSAIDs

Hypertension, diabetic mellitus, hyperlipidemia, and use of NSAIDs may affect renal outcomes, thus stratification analysis was performed based on these four risk factors. All subjects were assigned to four groups as follows: group a, subjects without risk factors; group b, subjects with one risk factor; group c, subjects with two risk factors, and group d, subjects with three risk factors. There were no subjects with four risk factors. A total of 30 (29.40%), 37 (36.30%), 30 (29.40%), and 5 (4.90%) subjects were assigned to groups a, b, c, and d, respectively. Mean SU, sCr, and eGFR levels for each group are presented in Table 2. SU was significantly reduced in all groups ($P < 0.05$), and

eGFR was improved in all groups. A statistically significant improvement of eGFR was shown in group a and group b ($P < 0.05$).

Moreover, subjects who used NSAIDs were excluded from further analysis. The remaining 94 (stage 2 CKD: 23 cases, stage 3 CKD: 66 cases, stage 4 CKD: 5 cases) subjects were analyzed. A significant improvement of eGFR was observed for 94 patients and stage 3 CKD patients (Fig. 3C and Table S3). The findings were similar to those for overall patients ($n = 104$). Among the 94 subjects, 37 reached the target SU ($SU < 360 \mu\text{mol/L}$). Obvious increases in eGFR were also observed in both the terminal $SU < 360 \mu\text{mol/L}$ group and terminal $SU \geq 360 \mu\text{mol/L}$ group ($P < 0.05$), with no between-group difference ($P > 0.05$) (Fig. 3D and Table S4).

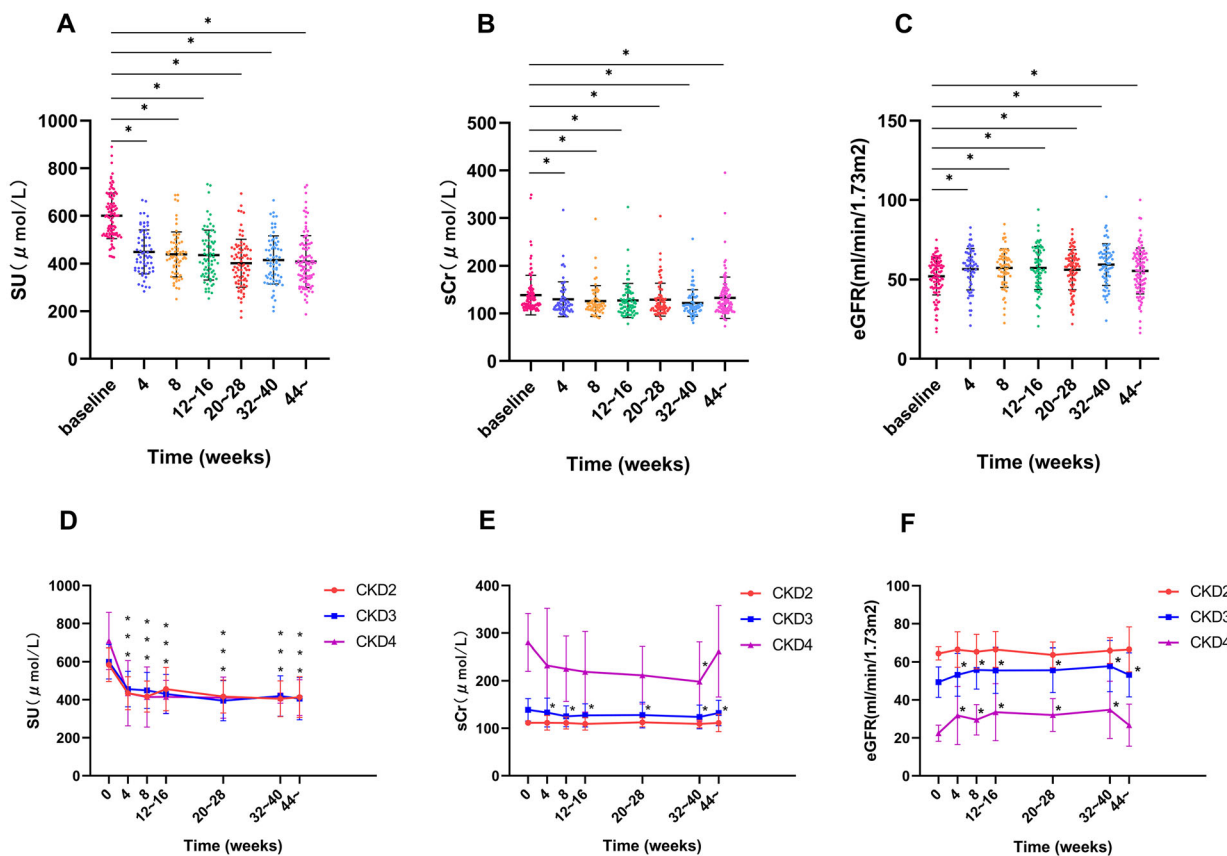


Fig. 2 levels of mean SU, sCr, and eGFR after ULT with febuxostat. **A** Mean SU levels of all subjects. **B** Mean sCr levels of all subjects. **C** Mean eGFR levels of all subjects. **D** Mean SU levels of subjects with different stages of CKD. **E** Mean sCr levels of subjects with different stages

of CKD. **F** Mean eGFR levels of subjects with different stages of CKD. **P* < 0.05, before versus after treatment (A–F). *SU* serum urate, *sCr* serum creatinine, *eGFR* estimated glomerular filtration rate, *ULT* urate-lowering treatment, *CKD* chronic kidney disease

BASELINE SU LEVEL AND BODY WEIGHT WERE CORRELATED WITH TARGET SU AS SHOWN BY LOGISTIC REGRESSION ANALYSIS AND SUBGROUP ANALYSIS

Univariate logistic regression analysis of the characteristics was performed to explore key variables that may affect the target SU. The findings showed that baseline SU level and body weight may be correlated with target SU (*P* ≤ 0.05, Table S5). Baseline SU, eGFR, body weight, and terminal dosage of febuxostat were include in multivariate logistic regression analysis on the basis of the results of the univariate

logistic regression analysis. The findings showed that baseline SU was correlated with target SU for febuxostat users in the current study, even after adjusting for confounding factors (Table 3; *P* < 0.05). Furthermore, we performed a subgroup analysis of RAT based on baseline SU level (< or ≥ 600 μmol/L) and body weight (≤ or > 70 kg). Patients with baseline SU level < 600 μmol/L or body weight ≤ 70 kg reached higher RATs than the overall patients (45.10%, 45.60%, versus 39.20%), respectively. When considering the two factors together, patients with baseline SU level < 600 μmol/L and body weight ≤ 70 kg exhibited higher RAT compared with the overall patients (56.70% versus 39.20%) (Fig. 3E and Table S6).

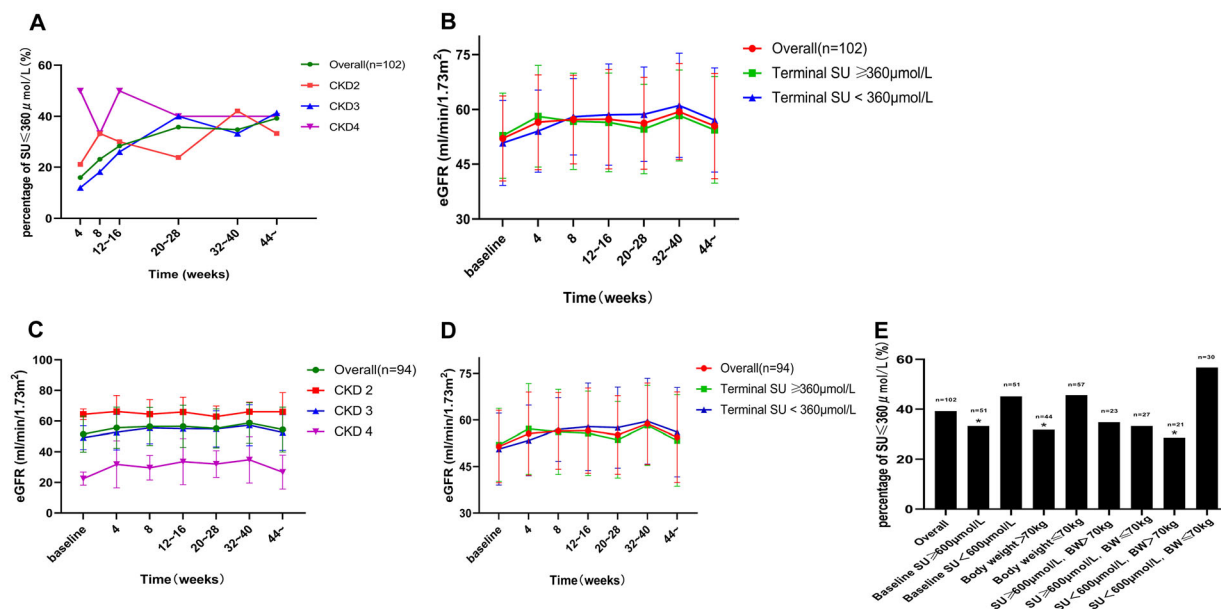


Fig. 3 Percentage achieving target SU (RAT) and mean eGFR in subgroup analysis. **A** RAT for overall patients and patients in different stages of CKD. **B** Levels of mean eGFR for overall patients and for patients in terminal SU < 360 $\mu\text{mol/L}$ group and terminal SU \geq 360 $\mu\text{mol/L}$ group. **C** Levels of mean eGFR for overall patients and patients in different stages of CKD after excluding patients with NSAIDs. **D** Levels of mean eGFR for overall patients and for patients in terminal SU < 360 $\mu\text{mol/L}$ group and

terminal SU \geq 360 $\mu\text{mol/L}$ group after excluding patients with NSAIDs. **E** RATs for patients in different subgroups (based on baseline SU level and body weight). * $P < 0.05$ versus RAT of baseline SU < 600 $\mu\text{mol/L}$ and BW \leq 70 kg, RAT rate of achieving target SU, SU serum urate, eGFR estimated glomerular filtration rate, CKD chronic kidney disease, NSAIDs non-steroidal anti-inflammatory drugs, BW body weight

DISCUSSION

This retrospective study has shown that febuxostat significantly reduces the SU concentrations and improves the renal function in patients with gout and CKD. Patients with stage 3 CKD, with \leq 1 risk factors (hypertension, diabetic mellitus, hyperlipidemia, or usage of NSAIDs) or with terminal SU < 360 $\mu\text{mol/L}$ present an obvious improvement of eGFR. Furthermore, baseline SU and body weight are correlated with achieving target SU in these patients. Patients with baseline SU < 600 $\mu\text{mol/L}$ and body weight \leq 70 kg could achieve higher RAT.

Febuxostat is the first-line ULT drug for patients with gout according to the Chinese gout clinical guidelines [20]. It is metabolized in the liver and excreted through the urinary system and intestinal tract [21], being more widely

used in patients with gout and CKD [22]. The current study indicates that febuxostat significantly reduced the SU concentrations in patients with gout and CKD. The results indicated that the SU concentration was decreased by approximately 200 $\mu\text{mol/L}$ for overall subjects and by 170–300 $\mu\text{mol/L}$ for different stages of CKD. The significant SU reduction remained against the background of different levels of risk factors. This result is relatively consistent with previous studies conducted in patients with gout and moderate-to-severe renal impairment [10].

Clinical evidence suggests that SU may increase the risk of new-onset CKD and intensify CKD progression [23, 24]. Studies have also investigated the potential association between ULT and kidney outcomes in patients with CKD and HUA. A large prospective study conducted in patients with stage 3 or 4 CKD and at high

Table 2 Stratification analysis of level of mean SU, sCr and eGFR on the basis of hypertension, diabetic mellitus, hyperlipidemia, and use of NSAIDs

Baseline	4 weeks	8 weeks	12–16 weeks	20–28 weeks	32–36 weeks	≥ 44 weeks
Group a (patients without risk factors, n = 30, 29.40%)						
SU	590.20 ± 89.36	460.80 ± 97.36*	446.19 ± 104.31*	433.56 ± 131.73*	396.22 ± 112.14*	431.05 ± 112.85*
sCr	132.09 ± 29.09	126.00 ± 28.11	112.31 ± 12.70	120.00 ± 28.46	124.58 ± 35.60	113.57 ± 25.29*
eGFR	54.52 ± 10.78	58.30 ± 12.31	63.42 ± 8.72	61.35 ± 14.76*	60.06 ± 14.60	65.09 ± 14.23*
Group b (patients with one risk factor, n = 37, 36.30%)						
SU	610.76 ± 107.22	440.38 ± 87.52*	440.63 ± 97.47*	449.87 ± 88.00*	430.69 ± 95.61*	418.96 ± 105.14*
sCr	147.16 ± 56.10	139.62 ± 50.32	134.08 ± 43.21*#	130.43 ± 45.94*	135.94 ± 42.79*	125.00 ± 34.74*
eGFR	49.80 ± 12.74	53.06 ± 13.54	54.61 ± 13.38*#	56.37 ± 13.14*	53.37 ± 12.85*	58.08 ± 13.24*
Group c (patients with two risk factors, n = 30, 29.40%)						
SU	591.00 ± 87.33	446.40 ± 99.50*	430.61 ± 88.62*	417.83 ± 104.27*	373.60 ± 95.11*	385.81 ± 77.38*
sCr	131.70 ± 29.47	124.95 ± 27.55	125.11 ± 21.98	129.20 ± 26.30	123.74 ± 22.78*	122.74 ± 20.83
eGFR	53.54 ± 10.69	57.51 ± 13.12*	56.17 ± 10.38	55.13 ± 13.03	56.81 ± 10.28*	57.74 ± 11.29
Group d (patients with three risk factors, n = 5, 4.90%)						
SU	648.80 ± 88.89	457.00 ± 72.13	439.75 ± 92.69*	457.00 ± 136.12	400.75 ± 82.94	477.00 ± 121.51
sCr	155.2 ± 34.30	112.50 ± 20.51	133.50 ± 37.08	122.33 ± 33.62	133.50 ± 22.96	135.75 ± 21.12
eGFR	44.83 ± 11.79	64.87 ± 14.69	54.59 ± 18.74	59.91 ± 18.32	53.02 ± 10.78	51.06 ± 11.89

Hypertension, diabetic mellitus, hyperlipidemia, and usage of NSAIDs are the four risk factors. Group a is defined as subjects who had none of four risk factors, group b as subjects who had one risk factors, group c as subjects who had two risk factors, and group d as subjects who had three risk factors. Data presented as mean ± SD

SU serum urate, sCr serum creatinine, eGFR estimated glomerular filtration rate, NSAIDs non-steroidal anti-inflammatory drugs

*P < 0.05, before versus after treatment

#P < 0.05, group b, c, or d versus group a

Table 3 Clinical factors related to achieving target SU according to multivariate logistic regression

Factor	Multivariate logistic regression		Adjusted ^{a*}		Adjusted ^{b*}	
	OR, 95% CI	P value	OR, 95% CI	P value	OR, 95% CI	P value
Body weight	0.952 (0.903–1.004)	0.069	0.954 (0.903–1.007)	0.088	0.953 (0.905–1.005)	0.076
Baseline SU	0.995 (0.990–0.999)	0.031	0.995(0.989–0.999)	0.039	0.995 (0.990–0.999)	0.037
Baseline eGFR	0.992 (0.952–1.034)	0.699	0.993 (0.950–1.038)	0.762	0.992 (0.952–1.034)	0.717
Terminal dosage of febuxostat	1.016 (0.992–1.040)	0.196	1.017 (0.992–1.043)	0.187	1.014 (0.990–1.040)	0.261

SU serum urate, eGFR estimated glomerular filtration rate, OR odd ratio, CI confidence interval

^{a*}Adjusting the multivariate logistic regression analysis by age, hypertension, diabetic mellitus, hyperlipidemia, cardio-cerebrovascular disease, and follow-up time

^{b*}Adjusting the multivariate logistic regression analysis by tophus and gout flares after treatment

risk of progression showed that ULT with allopurinol did not improve eGFR significantly as compared with placebo [25]. However, those results cannot be used to predict the kidney outcomes in patients with gout and CKD, as gout includes profound inflammation and chronic damage. In addition, evidence indicates that febuxostat may improve endothelial dysfunction, ameliorate inflammation, and reduce signal transduction of renal fibrosis and is more likely to benefit renal function than allopurinol [26–29]. Some clinical studies have indeed explored the relationship between ULT with febuxostat and eGFR change in patients with gout and CKD. A placebo-controlled study performed in patients with gout and moderate-to-severe renal impairment for 12 months found no significant change in renal function (least-squares mean for eGFR change of $-0.86 \text{ mL/min/1.73 m}^2 \sim 0.33 \text{ mL/min/1.73 m}^2$) [10]. A similar phenomenon occurred in a retrospective study conducted in stage 4/5 CKD patients (eGFR: $21.6 \text{ mL/min/1.73 m}^2$ versus $20.5 \text{ mL/min/1.73 m}^2$) [9]. Conversely, Kim observed an improvement in eGFR $< 30 \text{ mL/min/1.73 m}^2$, but the difference was not significant (eGFR: $19.84 \text{ mL/min/1.73 m}^2$ versus $23.49 \text{ mL/min/1.73 m}^2$) [30]. Only one small, multicenter observational retrospective study reported that XOIs could help conserve and improve renal function in patients with gout and stage 3 CKD,

but that study did not explore the effect of febuxostat separately [31]. Collectively, these findings are controversial and limited by sample size, study design, and populations. The effect of ULT with febuxostat on renal function remains obscure. In the present study, we observed that febuxostat could improve eGFR in patients with gout and CKD over a 44-week period, especially in those with stage 3 and 4 CKD. In addition, stratification analysis showed that patients with ≤ 1 risk factors had a relatively obvious improvement. Although a meta-analysis conducted by Sharma et al. reported that significantly greater improvement in eGFR and sCr was observed in patients treated with febuxostat for ≥ 1 year as compared with < 1 year [32], the follow-up time did not seem to affect the overall eGFR improvement in the present study.

An important finding of this study is that participants with gout and CKD could achieve $\text{SU} < 360 \mu\text{mol/L}$ with febuxostat monotherapy and that participants who achieved target SU benefited from an obvious improvement of eGFR. The target of $\text{SU} < 360 \mu\text{mol/L}$ is recommended for patients with gout according to the updated 2016 EULAR recommendations and 2020 ACR guidelines [14, 15], and this study may provide further evidence for the benefit of “treat to target” therapy with febuxostat in patients with gout and CKD.

Furthermore, the RAT of febuxostat in patients with gout and CKD was also evaluated. In the current study, the overall RAT showed an increase during the follow-up period, reaching a maximum of 39.20% at the end of the study. This RAT is similar to values reported in cohort studies or randomized controlled trials (RCTs) (febuxostat 20–80 mg/day) performed in patients with renal impairment as well as gout or HUA, where the RAT ranged from 22.50% to 71.70% [10, 16, 33–35]. For patients with CKD of different stages, the RATs varied from 33.30% to 41.40%. The RAT for patients with stage 3 or 4 CKD was higher than for stage 2 CKD. Logistic regression analysis and subgroup analysis revealed that body weight and baseline SU correlated with achieving target SU in patients with gout and CKD. This is partially consistent with previous studies on patients with gout, where baseline SU level was identified as a significant predictor of achieving target SU [16, 36]. Our finding addresses the lack of evidence in patients with gout and CKD in clinical practice and suggests that baseline SU is an important factor when predicting the achievement of target SU. Moreover, for patients with baseline $SU \geq 600 \mu\text{mol/L}$ or body weight $> 70 \text{ kg}$, dose escalation or combination medications may be needed to achieve target SU. These findings are important for the management of patients with gout and CKD.

This study has some strengths, including a complete screening protocol and relatively good participant retention, which lead to an increase in the overall RAT and a sustained reduction in SU level. However, there are several limitations to this study. Firstly, the imprecision and biases inherent to its retrospective study are great, and the actual adherence to or continuation with febuxostat cannot be validated, given that patients with gout have the worst drug adherence among all patients with chronic illnesses [37]. Despite this, our study found a sustained reduction in SU level and an increase in overall RAT. Secondly, the study only included male patients. Even though women with gout are much more likely to have CKD, data indicate that the prevalence of gout in females is lower than that in males and the pathogenic mechanism of gout in females is slightly

different from that in males [38–41]. Importantly, women develop gout at an older age and have more associated comorbidities [42]. Therefore, our results cannot be applied to female patients. Thirdly, the use of a serum creatinine-based equation to calculate the eGFR is another limitation. Although creatinine- and cystatin C-based equations or endogenous creatinine clearance rate (Ccr) is more accurate [43], it was not possible to test these because sCr was the primary detection parameter during the follow-up period while data for cystatin C and Ccr were lacking. Moreover, the cause of CKD was obscure due to a lack of a precise diagnostic approach, which restricts the analysis of the therapeutic effect of febuxostat in CKD with different primary diseases. Finally, such findings from a single-center study may not be generalizable, because of the heterogeneity of the study population.

In addition, we also checked the records of all 849 patients and found that about 747 (~88%) of them were excluded from the analysis. The main reason for exclusion was loss to follow-up or a lack of laboratory data records (~51%), indicating poor compliance, irregular or inadequate medication, or even withdrawal. This condition may affect the therapeutic effect of febuxostat and lead to an underestimate of outcomes. Importantly, the reason for loss in patients with gout was less likely to be failure to achieve SU reduction in clinical practice. In retrospective studies, loss to follow-up is a common occurrence and a challenge to overcome. In the future, additional, rigorously designed cohort studies or RCTs will be required to further confirm the findings of the current research.

CONCLUSIONS

In patients with gout and CKD, ULT with febuxostat significantly reduces SU levels and could improve renal function. Significant improvement in renal function was achieved in patients with stage 3 CKD, without hypertension, diabetic mellitus, hyperlipidemia, or usage of NSAIDs. A “treat to target” therapy with febuxostat could obviously improve renal

function. Besides, patients with baseline SU < 600 $\mu\text{mol/L}$ and body weight ≤ 70 kg were more likely to achieve target SU.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the Helsinki Declaration and in full compliance with current legislation for retrospective studies. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of medicine (approval No. 2021-0409). The requirement for written informed consent was waived by the Ethics Committee owing to the retrospective nature of the study.

Data Availability. All data generated or analyzed during this study are included in this article. Further information is available from the corresponding author on reasonable request.

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